

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61L 27/00, A61K 6/097	A1	(11) International Publication Number: WO 98/44964 (43) International Publication Date: 15 October 1998 (15.10.98)
(21) International Application Number: PCT/FI98/00283 (22) International Filing Date: 30 March 1998 (30.03.98) (30) Priority Data: 971385 4 April 1997 (04.04.97) FI (71) Applicants (for all designated States except US): BIOXID OY [FI/FI]; Ilkka Kangasniemi, Kõydenpunojankatu 2 B 5, FIN-20300 Turku (FI). CELLOMEDA OY [FI/FI]; Tykistökatu 6 A, FIN-20520 Turku (FI). (72) Inventors; and (75) Inventors/Applicants (for US only): ANDERSSON, Örjan [FI/FI]; Furuskogsvägen 58 A, FIN-65280 Vasa (FI). LÖNNQVIST, Kurt [FI/FI]; Nylandsgatan 12 B 30, FIN-20500 Åbo (FI). YLI-URPO, Antti [FI/FI]; Värtinäkätu 17, FIN-20660 Littoinen (FI). VILJANTO, Jouko [FI/FI]; Terhokatu 18, FIN-20720 Turku (FI). (74) Agent: TURUN PATENTTITOIMISTO OY; P.O. Box 99, FIN-20521 Turku (FI).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: A BIOCOMPATIBLE COMPOSITION, METHODS FOR ITS PREPARATION AND USES THEREOF (57) Abstract The invention relates to a biocompatible composition. The composition comprises a porous material of a bioresorbable organic polymer with hydroxyl- and/or carboxylic acid groups, and a bioactive material. According to one alternative, said bioactive material is distributed within said porous material. In this case said bioactive material can be present i) as particles embedded in said porous material, wherein said porous material is a spongy cellulose material, and/or ii) as a Si-gel derived from a solution containing a silicon compound, said solution having been brought into contact with the porous material. According to another alternative, said porous material is a spongy cellulose material and shaped to a reservoir encompassing particles of or a gel of said bioactive material. Methods for its preparation as well as to uses thereof are also included in the invention.		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav	TM	Turkmenistan
BF	Burkina Faso	GR	Greece		Republic of Macedonia	TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's	NZ	New Zealand		
CM	Cameroon		Republic of Korea	PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

A BIOCOMPATIBLE COMPOSITION, METHODS FOR ITS PREPARATION
AND USES THEREOF

FIELD OF THE INVENTION

This invention relates to a novel biocompatible composition comprising a bioactive material added to a porous material of a bioresorbable organic polymer. Furthermore, the
5 invention relates to methods for the preparation of said composition and to uses thereof.

INTRODUCTION AND BACKGROUND OF THE INVENTION

The publications and other materials used herein to illuminate the background of the invention, and in
10 particular, cases to provide additional details respecting the practice, are incorporated by reference.

A bioactive material is biocompatible and has affinity for living tissue. Traditional bioactive materials, such as bioactive glass and hydroxylapatite are rigid. These can be
15 used as bulk specimens, coatings or as granules or powders. An advantage of granules and powders is that they can be used in irregular bone defects or tissue structures. Thus, bioactive glass and hydroxylapatite granules are used to replace bone and to fill bony defects. Granules can also be
20 used around teeth to stabilise them.

Considering bioactive materials such as bioactive glass granules as an example, these have some advantages and some disadvantages. The advantages are easy handling of the granules and good osteoconductivity and bone bonding
25 ability. A major disadvantage which limits the use of bioactive materials is their lack of flexibility. A solid glass implant, for example, cannot be bent to fit an irregular defect. If granules are used there is a risk that they may migrate from the implantation site. Even if a

solid piece of glass can be shaped with a diamond burr, it would be advantageous to have a material which simply could be cut with a pair of scissors in the operating theatre. In order to achieve a good fit in the implantation site it would be an advantage if the material would expand after being put into place. This cannot be achieved with known bioactive glasses, hydroxylapatite, or any other known bioactive material. Another disadvantage of bioactive glass in some applications is their slow resorption. An ideal implant material would only provide a scaffold for bone growth and then disappear when the healing is complete. A bioactive glass which has proven successful as a bone filler in the form of granules is the one called S53P4 (1). However, the glass is only slowly resorbed when used as granules of 300 - 500 μm size. If the particle size is reduced, the surface area is correspondingly increased and a more rapid dissolution or resorption follows. However, smaller particles give stronger increase in pH, which may change the surface reactions of the glass in a direction unfavourable for bone formation. Therefore, it appears difficult to increase the resorption rate of the bioactive glass without compromising the biological performance.

OBJECTS OF THE INVENTION

The object of the present invention is a composition providing a solution to the above discussed draw-backs of bioactive glass and other known bioactive materials as well as implants made thereof.

In comparison with traditional bioactive implant materials the present invention provides a number of advantages:

- The composition is flexible and can be compressed and fitted to irregular bone defects.
- The composition can be cut to appropriate size and shape in the operation theatre, using a pair of scissors or a scalpel.
- The composition can be made in versions that swell after

implantation and thus, becomes immediately fixed.

- The spongy structure of the composition and the implant made thereof facilitates bone ingrowth and eventually total replacement of the implant with bone.
- 5 - The composition provides a sufficiently small total surface area and pH increase even if small (thus rapidly resorbing) glass particles are used.

Additional advantages of the composition according to the invention are:

- 10 - The composition is easy to handle.
- The composition can be made in a form that acts as a source for soluble silicon. Soluble silicon has been reported to stimulate bone formation. In addition to being essential for the bonding of a bioactive glass to bone,
- 15 silica is also a constituent of many biological systems (2). Carlisle showed that silica is essential for the development of bone (3). Recent reports suggest metabolic function (4) and intracellular mitogenic effects (5) of soluble silicon. These aspects were recently discussed by
- 20 Hench (6).
- The release rate can be controlled by choice of process parameters or by choice of appropriate bioactive material (e.g. choice of compositions of glass or gel).
- As a silicic acid releasing device, the composition can
- 25 be used for treatments involving remineralisation or mineralisation of tissue, for example of dentine.

SUMMARY OF THE INVENTION

- Thus, according to one aspect this invention provides a biocompatible composition, wherein said composition
- 30 comprises a porous material of a bioresorbable organic polymer with hydroxyl- and/or carboxylic acid groups, and a bioactive material,
 - wherein said bioactive material is distributed within said porous material, wherein
 - 35 i) said bioactive material is present as particles

- embedded in said porous material, and said porous material is a spongy cellulose material, and/or
- ii) said bioactive material is present as a Si-gel derived from a solution containing a silicon compound,
- 5 said solution having been brought into contact with the porous material, or
- wherein said porous material is a spongy cellulose material and shaped to a reservoir encompassing particles of or a gel of said bioactive material.
- 10 According to another aspect this invention provides an implant or a device for use in the treatment of sensitive teeth comprising a composition according to this invention. Said implant or device has the form of
- fibres,
- 15 - non-woven granules or pellets, a non-woven block, rod, sheet, membrane, tread, filter, foil, tube or coating; or
- a woven structure such as a sheet, a membrane, a filter, a sock, a tube or a coating.
- Furthermore, this invention concerns a method for the
- 20 preparation of a composition as defined above, said method comprising the steps of
- mixing particles of the bioactive material with a slurry of fibres of a cellulose material and one or more auxiliary substances necessary to convert said fibres into a porous
- 25 spongy material, and
- allowing said fibres and said auxiliary substance or substances to form the porous spongy material.

According to yet another aspect, this invention concerns a method for the preparation of a composition as defined

30 above, said method being characterized in that the porous material of a bioresorbable organic polymer with hydroxyl- and/or carboxylic acid groups is immersed into a solution containing a silicon compound, whereafter the silicon is brought into the form of a gel, after which the immersed

35 product optionally is acidified, pressed (or pressed,

acidified) and dried.

According to yet another aspect, this invention concerns a method for the preparation of a composition as defined above, said method being characterized in that

- 5 - particles of the bioactive material are mixed with a slurry of fibres of a cellulose material and one or more auxiliary substances necessary to convert said fibres into a porous spongy material,
- said fibres and said auxiliary substance or substances
- 10 are allowed to form the porous spongy material,
- the porous material containing particles of bioactive material is immersed into a solution containing a silicon compound, whereafter the silicon is brought into the form of a gel, after which the immersed product optionally is
- 15 acidified and then pressed and dried.

Furthermore, this invention concerns the use of a composition or an implant or a device as defined above for replacement of bone and/or filling of bone defects, for mineralisation of tissue such as dentine for treatment of

20 sensitive teeth, for stabilisation of teeth, for stabilisation of an implant, for replacement or augmentation of cartilage or for use in soft tissue surgery.

Furthermore, this invention concerns the use of a

25 composition or an implant or a device as defined above for clinical applications to replace bone grafts to 1) substitute bone defects in all areas of orthopedics, neurosurgery, ENT-surgery and dentistry; 2) stimulate fracture healing, especially in case of pseudoarthrosis; 3)

30 to create cancellous bone in soft tissues for grafting purposes; or 4) to speed up osteosynthesis.

Furthermore, this invention concerns the use of a composition or an implant as defined above or an implant as a carrier for drug delivery.

DETAILED DESCRIPTION OF THE INVENTION

In the following the term "biocompatible composition" shall be understood to mean a composition that is physiologically acceptable when brought into contact with body fluids and
 5 body tissue.

"Bioactive materials" refer to materials that are able to bind with body tissue and shall be understood to cover bioactive glasses, bioactive ceramics, glass ceramics and silica gels.

10 Bioactive glasses refer to amorphous mixtures of Si-oxide or Si-hydroxide with oxides of one or more elements such as sodium, potassium, calcium, magnesium, boron, titanium, aluminium and phosphorus. Some of the typical bioactive glass compositions are presented in Table 1.

15 Table 1. Composition (weight-%) of some bioactive glasses

<u>Designation</u>	<u>Na₂O</u>	<u>CaO</u>	<u>P₂O₅</u>	<u>B₂O₃</u>	<u>Al₂O₃</u>	<u>SiO₂</u>
S53P4	23.00	20.00	4.00	0.00	0.00	53.00
S45P7	24.00	22.00	7.00	2.00	0.00	45.00
S55.5P4	29.00	11.00	4.00	0.00	0.50	55.50

20 Bioactive ceramics are crystalline materials such as calcium phosphates and calcium carbonate.

Bioactive glass ceramics are composites comprising crystals embedded in an amorphous phase.

25 The wording "porous material" referred to hereinafter is a material enabling blood vessels to penetrate the same. Therefore, the material shall have an open pore structure and a pore diameter of at least 100 µm, preferably at least 500 µm (7).

The organic polymer forming the bioresorbable porous material is preferably a polysaccharide such as cellulose, a cellulose derivative, partially decomposed cellulose or cellulose derivative, starch, and the like.

5 The compositions containing the bioactive material mainly in the form of particles is called a composition of "Type A" in the following. The bioactive material in the form of particles is preferably a bioactive glass, e.g. one of those listed in Table 1. The bioactive glass coded S53P4 is
10 particularly preferred.

The compositions comprising bioactive material in the form of a Si-gel derived from a solution containing a silicon compound is in the following called a "Type B" composition. This composition could optionally also contain bioactive
15 material in the form of particles. Thus, a Type A composition can be treated with a solution containing a silicon compound to give a Type B composition.

It should be noted that both compositions (Type A and Type B), although differing in structure and manufacturing, have
20 similar properties and can be used for similar purposes.

The ratio of bioactive material : amount of porous material should preferably be at least 1:1, most preferably about 4:1.

In a Type A composition the amount of bioactive particles
25 should preferably vary in the range 50 - 99.9 weight-%.

Description of a Type A composition

In developing a Type A composition containing bioactive glass as the bioactive material and cellulose as the porous material a number of different particle size fractions and
30 amounts of glass were studied. The particles could not be introduced into the finished porous material of cellulose,

but they had to be added during the stage of manufacturing of the porous cellulose material from its raw materials. The manufacturing process had to be optimised in order to avoid adverse chemical changes in the glass, which could
5 have potential negative effects on the biological performance. The optimum particle amount was chosen on basis of manufacturing aspects and aspects of particle-to-particle distances. The resulting composition can be easily cut to appropriate size and shape, it is flexible and it
10 expands by absorbing water or tissue fluid. The content of inorganic bioactive material is sufficient to have a stimulatory effect on bone growth, yet low enough to facilitate sufficiently rapid resorption.

The retention of particles in the cellulose is generally
15 good, although some particles may loosen when the material is cut. By acid treatment the surface of the glass particles can be transformed to silica gel with a high surface concentration of hydroxyl groups. It should be recognised that one special feature of cellulose is its strong
20 tendency to form hydrogen bonds with neighbouring cellulose molecules. Also intramolecular hydrogen bonds form. Thus, in addition to mechanical retention, the hydrogen bonding capacity of the cellulose also facilitates attachment between cellulose and the Si-gel surface of bioactive glass
25 particles. Another method to further improve the retention of the glass particles in the cellulose is by causing a Si-gel to be formed therein, said Si-gel having been derived from a solution of a silicon compound. This is discussed later as a combination of the compositions of Type A and
30 Type B according to the present invention.

Description of a Type B composition

Compositions of Type B comprise a porous material e.g. based on cellulose which after their normal manufacturing have been given an additional treatment with a solution
35 containing a silicon compound. Thus, the cellulose material

(or the like) is immersed in a solution which contains silicon in the form of silicate ions (water-glass), silicic acid or silica gel (e.g. acidified water-glass) or in the form of organic silicon containing compounds (sol-gel precursors). Common to all silicon sources is that they are subsequently treated to transform them into silica gel.

The high pH of alkali silicate solutions (water-glass) may have negative effects on the biological response. By acidification Si-gel forms and the pH of the material is reduced. Silicic acid can also be made to precipitate by adjusting pH or by adding ions such as calcium. The organic silicon compounds may be transformed to silica gel by the sol-gel process. Regardless of the source of silicon and the manufacturing technique, the final composition consists of a cellulose material impregnated with silica gel. The Si-gel serves two purposes. Si-gel is known to be highly biocompatible and thus, to have advantages as an implant material. Si-gel also dissolves slowly in the tissue and silicic acid is released. In addition to being essential for the bonding of a bioactive glass to bone, silica is also a constituent of many biological systems (2). Carlisle showed that silica is essential for the development of bone (3). Recent reports suggest metabolic function (4) and intracellular mitogenic effects (5) of soluble silicon. These aspects were recently discussed by Hench (6).

The capacity of the Type B composition to release soluble silicon can also be used in applications where silicic acid or silicate ions are to be transferred into tissue in order to induce mineralisation. One such example is the use of composition B as a device for treating sensitive teeth (with open dentine tubules), described in (8).

It shall be stressed that the experimental findings for the Type A and Type B compositions reported here also will apply to other compositions of these types where cellulose and the bioactive glass are replaced by other organic

polymers and bioactive materials within the scope of this invention.

Type C composition

According to this alternative, the porous material of the
5 organic polymer is shaped to a container, which can be flexible or stiff. Said container is then filled with particles of or a gel of the bioactive material.

Manufacturing of Type A compositions

In combining a highly porous, flexible and expandable
10 cellulose material (or other organic polymer material) with a bioactive particulate material several problems had to be solved. In the below referred work the bioactive particulate material used was bioactive glass and the porous material was a cellulose sponge. The glass must not
15 undergo adverse changes in the manufacturing process. Thus, both the glass and the composite manufacturing process must be chosen so that problems are avoided. The glass must also show sufficient retention within the cellulose material. Otherwise, the composition will not remain isotropic, but
20 bioactive particles may be lost in some parts of the composite due to mechanical loads. To a small extent particles may loosen from Type A composition during cutting in the dry state. However, no changes in the particle distribution within the composite were observed. Thus, the
25 composition was isotrope.

In compositions of Type A the bioactive particles are introduced in a slurry of a bioresorbable organic polymer fibres as defined before, and one or more auxiliary substances useful to convert said fibres into a porous
30 material (e.g. cellulose fibres and viscose). In this way the organic molecules can attach around the irregular shape of the particles. Through hydrogen bonding the retention is probably improved as compared to particulate materials and

organic materials without the exceptionally large amounts of hydroxyl groups characteristic of cellulose and Si-gel.

Manufacturing of a Type B composition

The first version of Type B composition was developed by
5 using a sodium silicate solution (water-glass) and a viscose cellulose sponge. A cellulose sponge is particularly advantageous due to its high porosity. The following parameters were studied:

- different dilutions of water-glass, i.e. different
10 silicate ion concentrations and pH
- the amount of water-glass in the sponge (pressed or not pressed after immersion in water glass)
- the role of acidification (strength and volume of acid used)
- 15 - the drying process (in air at room temperature, at elevated temperature, freeze-drying)

Several problems were encountered. By immersing the sponge in the alkaline silicate solution (water-glass) and subsequent drying, a composition was obtained that
20 contained a great amount of silicate ions. When immersed in an aqueous solution or in living tissue the dissolving sodium silicate strongly increased the pH in its surroundings. This is not acceptable from a biocompatibility point of view. The problem with the
25 alkaline effect of the implant should in principle be possible to avoided by acidifying the water glass containing cellulose material. However, when the alkaline water-glass containing sponge was immersed in the acid, the water glass dissolved into the acid and formed Si-gel in
30 the solution, rather than in the sponge. By experiments with different acid strengths and volumes it was possible to avoid the extensive dissolution of silicate ions into the acid solution. Instead the Si-gel precipitated within the sponge. The Si-gel impregnated sponge was subsequently

dried. Also the drying process had to be optimised, since the Si-gel dried very slowly at room temperature and humidity. This is not surprising since Si-gel can be used as a desiccant due to its water absorbing capacity. The method finally chosen was drying at a slightly elevated temperature.

The compositions according to the invention and their preparation is described more in detail in the following non-limiting examples.

10 Example 1

Preparation of a Type A composition

A cellulose viscose solution containing 5 % of cellulose was prepared according to known methods. Calculated on the weight the cellulose, 20 % of cotton fibres cut to 8 - 10 mm length was mixed into the viscose. A pore-forming material $\text{Na}_2\text{SO}_4 \cdot 10 \text{H}_2\text{O}$ (Glauber's salt) with a particle size $< 1.0 \text{ mm}$ was used. This Glauber's salt was mixed with bioactive glass having a grain size of $0,14 - 0,20 \text{ mm}$. The bioactive glass used was the glass designated S53P4 in Table 1. Pore-forming material was added 80 times and bioactive glass 5 times the initial weight of the cellulose. The material obtained was placed into a mold and the cellulose was regenerated by heating in a waterbath. The crude cellulose sponge containing bioactive glass leaving the waterbath was washed salt free by means of hot water, treated with dilute acid, bleaching solution and finally washed repetitively with distilled water. The product was then dried, cut to desired size and packed.

Example 2

30 Preparation of a Type B composition

A cellulose sponge, without bioactive glass, was prepared

according to example 1. The cellulose sponge was soaked in a 15 % solution of water glass, transferred to an acid solution, removed therefrom, dried, cut to desired size and packed.

5 Example 3

Preparation of a Type B composition comprising particles of a bioactive material

A cellulose sponge was prepared according to example 1. The cellulose sponge containing bioactive glass was soaked in a
10 6 % solution of water glass, transferred to an acid solution, removed therefrom, dried, cut to desired size and packed.

In vitro tests

The materials were tested by immersion in simulated body
15 fluid (SBF). This solution contains inorganic ions in concentration close to those on plasma. The solution was Tris-buffered with 50 mM tris(hydroxymethyl-aminomethane) and 45 mM HCl. The solution pH was 7.4 and the temperature 37 °C. Test periods were 1, 3, 7, and 14 days. After the
20 test, the samples were removed, dried and prepared for scanning electron microscopy. It was found that the sponges which had been treated with diluted water-glass solutions (total silica content of 3, 6 or 15 %) lost most of their Si-gel within some days. Thus, rapid short-term release was
25 achieved. For the high concentration water-glass (30 %, i.e not diluted) treated sponges surprising phenomena were observed. For the sponges which had not been pressed in order to remove excess water-glass prior to acidification, Si-gel was evenly distributed within the structure of the
30 cellulose sponge. The Si-amount in the sponge decrease with time during the 14 day dissolution test. For the sponges which had been pressed to remove excess water-glass prior to acidification, a dense looking silicon containing layer

formed. This layer did not change much during the 14 day dissolution test, as observed by scanning electron microscopy. Thus, pressing the high concentration water-glass treated sponge resulted in a composition with a lower total Si-content and a slower release of this content as compared with the corresponding not pressed sponge. The latter sponge had a higher amount of Si-gel prior to dissolution testing, but a lower amount after the 14 day dissolution test. Thus, for the same water-glass concentration in the immersion solution, the Si-release rate of the resulting composition can be adjusted by changing the extent to which the cellulose material is pressed. A high rate, high total amount, short-term release device as well as a low rate, lower total amount, long-term release device can be obtained. Devices with intermediate release rates, total amounts and life times (i.e. release duration) can be obtained by varying the extent to which the cellulose material is pressed prior to acidification.

Advantages of the composition

When the cellulose material has been impregnated with water-glass, acidified and dried it has become somewhat rigid. The mechanical strength reduces the risk for movements/flexing and associated cracking and loosening of Si-gel fragments. The implant softens if immersed in water or saline prior to implantation. In the wet state it can be easily compressed and fitted into irregular implantation sites.

A particularly advantageous and surprising feature of the composition according to this invention is that it can be compressed and shaped also in its dry state. Thus, after drying, the composition can be shaped for example to a thin plate. The compressed shape remains until the implant is moistened before or after implantation. Thin plates, foils, membranes, filters can be prepared in the wet state and further shaped to e.g tubes in the dry state.

A likewise advantageous and surprising feature is that even the cellulose (or other organic polymer as defined above) with the highest Si-gel content, could easily be cut with a pair of scissors or a scalpel. In fact, cutting the Si-gel
5 containing compositions was easier than cutting the pure cellulose sponge.

The wet process can be realised both as a batch process and a continuous one. The continuous process may be similar to that in a paper machine. The cellulose material (or other
10 organic polymer as defined above) is collected from the solution on a wire mesh, transported by rollers through an alkali silicate bath, followed by an acid bath (saturated with soluble silicon) and finally it is dried. The composition can also be cut to appropriate shape and size
15 in its moist state.

Compositions of the present invention can be prepared in many forms such as non-woven blocks, rods, granules/pellets, sheets, threads, membranes, filters, tubes and coatings. The composition can also be in the form
20 of fibres and woven structures such as sheets, membranes, filters, socks, tubes and coatings.

Modification of compositions of Type A and Type B

An additional advantage of the compositions according to the invention, is that the cellulose (or other organic
25 polymer as defined above) can be broken down (e.g. by oxidative bleaching or by radiation) to different extents, either before or after the addition of the bioactive material. This will result in different degradation rates in the tissue. Thus, the degradation rate for the cellulose
30 (or the like) can be adjusted to fit that of the Si-release duration of the composition of Type B or the bioactive particle resorption rate of composition of Type A. Similarly, the resorption of the inorganic bioactive material (e.g. glass or gel) can be adjusted by choice of

composition, manufacturing parameters, particle size and amount of said material.

The compositions of Type A and Type B can be used as such or combined with biologically or therapeutically active
5 molecules and substances. Such active substances may for example be drugs, antibiotics, hormones, growth factors or other organic compounds. Also inorganic ions may be incorporated into the composition. The inorganic ions can either attach to the cellulose due to its ion exchange
10 capacity, or they may be incorporated into the Si-gel. Inorganic ions may have beneficial effects on bone mineralisation as well as on mineralisation of the implant material. By doping the gel in its manufacturing stage it is also possible to affect its resorption rate. As examples
15 of doping agents can be mentioned stabilising ions such as calcium, magnesium and iron.

The mechanical properties can be affected by introducing some reinforcing or modifying phase. In the present work cotton fibres were used. Other example of reinforcing
20 materials are other cellulose fibres, synthetic biodegradable fibres based on polylactide, polyglycolide, polyhydroxybutyrate, or synthetic inorganic fibres, filaments or whiskers such as glass or Si-gel fibres prepared by the sol-gel method. Common to all fibres is
25 that they with time should resorb.

The manufacturing process used for composition B according to the present invention can be applied as an additional treatment for composition Type A according to the present invention. Thus, the glass particle containing cellulose
30 (Type A) is treated with water glass or another Si-containing solution during or after manufacturing. The precipitated Si-gel basically provides the same advantages as in compositions of Type B, i.e. controlled Si-release and biocompatible surfaces for tissue growth. Additionally
35 the Si-gel further improves the adhesion between glass

particles and the cellulose fibres. By animal experiments it was found that the water-glass had no adverse effects on the tissue reactions when used as a glue between particles of bioactive glass.

- 5 In the experimental work described above a cotton reinforced viscose cellulose sponge was used. However, the present invention is not restricted to using these materials. A person familiar with the field will recognise that the present invention also can be applied to other
10 cellulose materials or modifications. The Si-impregnation technique can also be used to impregnate other biocompatible and bioresorbable porous material with some affinity for silica gel. The many hydroxyl groups of the cellulose molecule facilitates the attachment of Si-gel by
15 hydrogen bonding. Other biocompatible and bioresorbable organic materials with hydroxyl or carboxylic acid groups are expected to perform in the same way.

Uses for the compositions according to the invention

- Compositions of Type A, Type B, Type C and their
20 combination can be used in many different applications. The multi-purpose feature and the many additional advantages of the invention makes it different from known materials. Some examples of applications are given below.

- Replacement of bone and filling of bony defects
- 25 - Use for mineralisation of tissue, e.g. of dentine as a treatment for sensitive teeth (8).
- Use for stabilisation of teeth (composition placed around single teeth)
- Use for stabilisation of implants (placed between the
30 implant and the tissue)
- Use for replacement or augmentation of cartilage (joint surgery, maxillofacial and plastic surgery)
- Use in soft tissue applications
- Use as drug delivery device or as a part thereof
- 35 - Use in clinical applications instead of bone grafts to 1)

substitute bone defects in all areas of orthopedics, neurosurgery, ENT-surgery and dentistry; 2) stimulate fracture healing, especially in case of pseudoarthrosis; 3) to create cancellous bone in soft tissues for grafting
5 purposes; or 4) to speed up osteosynthesis.

It will be appreciated that the methods of the present invention can be incorporated in the form of a variety of embodiments, only a few of which are disclosed herein. It will be apparent for the specialist in the field that other
10 embodiments exist and do not depart from the spirit of the invention. Thus, the described embodiments are illustrative and should not be construed as restrictive.

REFERENCES

1. Ö.H. Andersson, G. Liu, K. H. Karlsson, L. Niemi, J. Miettinen, and J. Juhanaja, "In vivo behaviour of glasses in the $\text{SiO}_2\text{-Na}_2\text{O-CaO-P}_2\text{O}_5\text{-Al}_2\text{O}_3\text{-B}_2\text{O}_5$ -system", Journal of
5 Materials Science: Materials in Medicine, 1 (1990) 219-227.
2. Iler, R.K., "The chemistry of silica", John Wiley & Sons Inc, New York, NY., 1979.
3. Carlisle, E., In: Biochemistry of Silicon, Ciba
Foundation Symposium 121. John Wiley & Sons, New York, NY.
10 1986.
4. Keeting, P.E., Oursler, M.J., Wiegand, K.E., Bonde, S.K., Spelsberg, T.C., Riggs, B.L. J. Bone and Mineral Res. 1992, 7, 1281-1289.
5. Vrouwenwelder, W.C.A., Groot, C.G., de Groot, K., J.
15 Biomed. Mater. Res. 1993, 27, 465-475.
6. Hench, L.L., in: Bioceramics, Vol. 7, Ö.H. Andersson, R.-P. Happonen, and A. Yli-Urpo (Eds.), Butterworth-Heinemann Ltd., Oxford, 1994, 3-14.
7. O. Pajulo et al., Journal of Biomedical Materials
20 Research, Vol. 32 (1996) 439-446.
8. International Patent Application Publication No. WO 96/10985, Salonen et al.

CLAIMS

1. A biocompatible composition characterized in that it comprises a porous material of a bioresorbable organic polymer with hydroxyl- and/or carboxylic acid groups, and a bioactive material,
 - 5 - wherein said bioactive material is distributed within said porous material, wherein
 - i) said bioactive material is present as particles embedded in said porous material, and said porous material is a spongy cellulose material, and/or
 - 10 ii) said bioactive material is present as a Si-gel derived from a solution containing a silicon compound, said solution having been brought into contact with the porous material, or
 - wherein said porous material is a spongy cellulose
 - 15 material and shaped to a reservoir encompassing particles of or a gel of said bioactive material.
2. The composition according to claim 1 characterized in that the bioactive material comprises particles of a
- 20 bioactive glass.
3. The composition according to claim 1 or 2 characterized in that the solution containing the silicon compound is an alkali silicate solution.
4. The composition according to claim 1 characterized in
- 25 that the porous material comprising particles of the bioactive material has been immersed into a solution containing a silicon compound, whereafter the silicon has been brought into the form of a gel.
5. The composition according to claim 4 characterized in
- 30 that the porous material is a cellulose sponge, the bioactive material is bioactive glass and the solution containing the silicon compound is an alkali silicate

solution.

6. The composition according to any of claims 1 to 5
characterized in that the Si-gel is doped with one or more
agents able to affect the properties, such as the
5 resorption rate of the Si-gel.

7. The composition according to any of the claims 1 to 6
characterized in that said composition is reinforced with
organic and/or inorganic fibres.

8. The composition according to any of the claims 1 to 7
10 characterized in that it comprises one or more
therapeutically or biologically active agents.

9. An implant comprising a composition according to any of
the foregoing claims characterized in that said implant has
the form of
15 - fibres,
- non-woven granules or pellets, a non-woven block, rod,
sheet, membrane, thread filter, foil, tube or coating; or
- a woven structure such as a sheet, a membrane, a filter,
a sock, a tube or a coating.

20 10. A method for the preparation of a composition according
to claim 1 characterized in that
- particles of the bioactive material are mixed with a
slurry of fibres of the cellulose material and one or more
auxiliary substances necessary to convert said fibres into
25 a porous spongy material, and
- said fibres and said auxiliary substance or substances
are allowed to form the porous spongy material.

11. A method for the preparation of a composition according
to claim 1 characterized in that the porous material of a
30 bioresorbable organic polymer with hydroxyl- and/or
carboxylic acid groups is immersed into a solution
containing a silicon compound, whereafter the silicon is

brought into the form of a gel, after which the immersed product is optionally acidified, pressed and dried.

12. A method for the preparation of a composition according to claim 1 characterized in that
- 5 - particles of the bioactive material are mixed with a slurry of fibres of the cellulose material, and one or more auxiliary substances necessary to convert said fibres into a porous spongy material,
 - said fibres and said auxiliary substance or substances
 - 10 are allowed to form the porous spongy material,
 - the porous spongy material containing particles of bioactive material is immersed into a solution containing a silicon compound, whereafter the silicon is brought into the form of a gel, after which the immersed product is
 - 15 optionally acidified, and then pressed and dried.

13. Use of a composition according to any of the claims 1 to 8 for the manufacture of a preparation for replacement of bone and/or filling of bone defects, for mineralisation of tissue such as dentine for treatment of sensitive teeth,
- 20 for stabilisation of teeth, for stabilisation of implants, for replacement or augmentation of cartilage or for use in soft tissue surgery.

14. Use of a composition according to any of the claims 1 to 8 as a carrier for drug delivery.

- 25 15. Use of a composition according to any of the claims 1 to 8 for the manufacture of a preparation for clinical applications to replace bone grafts to 1) substitute bone defects in all areas of orthopedics, neurosurgery, ENT-surgery and dentistry; 2) stimulate fracture healing,
- 30 especially in case of pseudoarthrosis; 3) to create cancellous bone in soft tissues for grafting purposes; or 4) to speed up osteosynthesis.

16. A device for use in the treatment of sensitive teeth,

said device comprising a composition according to any of the foregoing claims characterized in that said device has the form of

- fibres,
- 5 - non-woven granules or pellets, a non-woven block, rod, sheet, membrane, thread filter, foil, tube or coating; or
- a woven structure such as a sheet, a membrane, a filter, a sock, a tube or a coating.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/FI 98/00283

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61L 27/00, A61K 6/097

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K, A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,N0 classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, EPODOC, PAJ, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0714666 A1 (ETHICON, INC.), 5 June 1996 (05.06.96) --	1-16
A	WO 8601113 A1 (BRINKS, GERRIT, JOHANNES ET AL), 27 February 1986 (27.02.86) -- -----	1-16

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

16 July 1998

Date of mailing of the international search report

1998 -07- 17

Name and mailing address of the ISA/
Swedish Patent Office
Box 5055, S-102 42 STOCKHOLM
Facsimile No. +46 8 666 02 86

Authorized officer

Carl-Olof Gustafsson
Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.

PCT/FI98/00283

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 14 is directed to a method of treatment of the human/animal body, the search has been carried out based on the alleged effect of the composition.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐

The additional search fees were accompanied by the applicant's protest.

☐

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

30/06/98

International application No.
PCT/FI 98/00283

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0714666 A1	05/06/96	AU 3795395 A	06/06/96
		BR 9505580 A	04/11/97
		CA 2164045 A	31/05/96
		JP 8215299 A	27/08/96
		US 5679723 A	21/10/97
		US 5747390 A	05/05/98
<hr/>			
WO 8601113 A1	27/02/86	EP 0191086 A	20/08/86
		NL 8402534 A	17/03/86
<hr/>			